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ORIGINAL RESEARCH

Noninvasive Advanced Cardiovascular Magnetic Resonance–Derived Fontan Hemodynamics Are Associated With Reduced Kidney Function But Not Albuminuria

Jef Van den Eynde , MD; Jos J. M. Westenberg , PhD; Mark G. Hazekamp , MD, PhD; Hildo J. Lamb , MD, PhD; Monique R. M. Jongbloed , MD, PhD; Jolanda J. Wentzel , PhD; Sasa Kenjeres , PhD; Ilona A. Dekkers , MD, PhD; Alexander Van De Bruaene , MD, PhD; Friso M. Rijnberg , MD*; Arno A. W. Roest , MD, PhD*

BACKGROUND: Kidney disease is the most important predictor of death in patients with a Fontan circulation, yet its clinical and hemodynamic correlates have not been well established.

METHODS AND RESULTS: A total of 53 ambulatory patients with a Fontan circulation (median age, 16.2 years, 52.8% male patients) underwent advanced cardiovascular magnetic resonance assessment, including 4-dimensional flow imaging and computational fluid dynamics. Estimated glomerular filtration rate (eGFR) <90 mL/min per 1.73 m² was observed in 20.8% and albumin-to-creatinine ratio >3 mg/mmol in 39.6%. The average eGFR decline rate was -1.83 mL/min per 1.73 m² per year (95% CI, -2.67 to -0.99 ; $P<0.001$). Lower eGFR was associated with older age, larger body surface area at examination, longer time since Fontan procedure, and lower systemic ventricular ejection fraction. Higher albumin-to-creatinine ratio was associated with absence of fenestration at the Fontan operation, and older age and lower systemic ventricular ejection fraction at the assessment. Lower cross-sectional area of the Fontan conduit indexed to flow ($r=0.32$, $P=0.038$), higher inferior vena cava–conduit velocity mismatch factor ($r=-0.35$, $P=0.022$), higher kinetic energy indexed to flow in the total cavopulmonary connection ($r=-0.59$, $P=0.005$), and higher total cavopulmonary connection resistance ($r=-0.42$, $P=0.005$ at rest; $r=-0.43$, $P=0.004$ during exercise) were all associated with lower eGFR but not with albuminuria.

CONCLUSIONS: Kidney dysfunction and albuminuria are common among clinically well adolescents and young adults with a Fontan circulation. Advanced cardiovascular magnetic resonance–derived metrics indicative of declining Fontan hemodynamics are associated with eGFR and might serve as targets to improve kidney health. Albuminuria might be driven by other factors that need further investigation.

Key Words: albuminuria ■ chronic kidney disease ■ computational fluid dynamics ■ Fontan ■ hemodynamics ■ kidney function ■ magnetic resonance imaging

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CLINICAL PERSPECTIVE

What Is New?

- Even in a young and otherwise clinically well cohort of adolescents and young adults with a Fontan circulation, 50.9% either had reduced kidney function (20.8%) or albuminuria (39.6%).
- Lower estimated glomerular filtration rate was clearly linked to various metrics indicative of declining Fontan hemodynamics, including smaller conduit size, higher resistances across the total cavopulmonary connection, and higher inferior vena cava–conduit velocity mismatch factor.
- High urine albumin-to-creatinine ratio was not clearly linked to these metrics. Albuminuria might therefore be driven by other factors, some of which might even occur before or directly after the Fontan procedure.

What Are the Clinical Implications?

- Advanced cardiovascular magnetic resonance allows for detailed examination of Fontan hemodynamics.
- Given the high prevalence of kidney disease among patients with a Fontan circulation, the institution of early and structured follow-up protocols will be required to improve outcomes.
- Our present study contributes to our understanding of the pathophysiology of kidney disease in patients with a Fontan circulation and offers promising targets for intervention (eg, Fontan conduit expansion) to improve kidney health in this population.

Nonstandard Abbreviations and Acronyms

ACR	albumin-to-creatinine ratio
CFD	computational fluid dynamics
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSA	cross-sectional area
IVC	inferior vena cava
mGFR	measured glomerular filtration rate
SVC	superior vena cava
TCPC	total cavopulmonary connection

Since the introduction of the Fontan procedure in 1968,¹ congenital heart defects characterized by single-ventricle physiology have progressed from being lethal conditions to becoming conditions that can be successfully managed. However, despite remarkable advancements in survival rates, a significant burden of morbidity persists among these patients.² The distinctive feature of the Fontan circulation

is the sustained elevation of central venous pressure, coupled with a reduction in cardiac output. This intricate interplay gives rise to a cascade of physiological consequences. Exercise intolerance, heart failure, arrhythmias, liver disease, kidney dysfunction, lymphatic disorders, and neuropsychiatric conditions are among the various ailments that accompany the deteriorating Fontan circulation.

Second only to thyroid dysfunction, kidney dysfunction stands out as the most prevalent extracardiac comorbidity in the Fontan population, occurring in up to half of these patients.³ A multitude of studies have implicated kidney dysfunction as one of the most important risk factors for death in adults with congenital heart disease, increasing the risk of death by 2- to 3-fold.^{4–6} Similar findings have been confirmed within the subgroup of patients with Fontan circulation.⁷ Despite widespread availability as key screening tools for chronic kidney disease (CKD), data regarding estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR) in patients with Fontan circulation remain limited.⁸ Furthermore, the determinants of kidney disease within the Fontan circulation have not been fully established. As a result, the key targets for interventions that aim to improve kidney health remain unclear.

Four-dimensional cardiovascular magnetic resonance (CMR) flow imaging is an emerging noninvasive tool that provides unique and comprehensive in vivo characterization of cardiovascular blood flow in a single acquisition.⁹ This technique can be further supplemented with computational fluid dynamics (CFD) to simulate complex hemodynamics, for instance, during exercise. Our group has leveraged advanced flow CMR, including real-time 2-dimensional and 4-dimensional flow, for further understanding of various aspects of total cavopulmonary connection (TCPC) hemodynamics in patients with a Fontan circulation.^{10–16} Our previous work has demonstrated correlations of 4-dimensional flow CMR metrics with lower exercise capacity and higher levels of liver fibrosis/congestion.^{15,16} Because venous congestion has been associated with kidney dysfunction in various clinical populations,^{17,18} we hypothesized that similar metrics reflecting adverse TCPC hemodynamics could be linked to worse kidney health in patients with a Fontan circulation. In the present study, we sought to investigate whether advanced CMR- and CFD-derived metrics were correlated with kidney function and albuminuria in a cohort of adolescents and young adults with a Fontan circulation.

METHODS

Data are available upon reasonable request.

Study Population

Sixty-two patients with a Fontan circulation were prospectively evaluated using a comprehensive CMR research protocol, including 4-dimensional flow imaging of the TCPC, between 2018 and 2021 at the Leiden University Medical Center, Leiden, the Netherlands. The study was approved by the medical ethical review board of the Leiden University Medical Center (P18.024). Written informed consent was obtained from all patients or their parents. All patients >8 years old without contraindications for CMR and a clinical indication for routine surveillance of the Fontan pathway using CMR were eligible for inclusion. Previous analyses of this cohort have been published before.¹⁹ Because the focus of the present study was to identify correlations of CMR- and CFD-derived metrics with kidney function and albuminuria, only the 53 patients who also had laboratory measurements of eGFR and ACR available were considered.

Kidney Assessment

Standard laboratory kidney assessment was performed on the same day or within 6 months of CMR and included eGFR (unit: mL/min per 1.73 m²) and ACR (unit: mg/mmol). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 40 equation was used to calculate eGFR on the basis of age, sex, and serum creatinine.²⁰ This equation first calculates an adjusted serum creatinine level for children and young adults aged <40 years with 40 as the assigned age, and then applies the CKD-EPI equation. This strategy makes the CKD-EPI equation applicable to the full spectrum of age and kidney function, has been validated in ages 2 up to 39 years, and has been shown to outperform the Schwartz-Lyon equation in children.²⁰ ACR was used to classify albuminuria as follows: no albuminuria (A1, <3 mg/mmol), microalbuminuria (A2, 3–30 mg/mmol), or macroalbuminuria (A3, >30 mg/mmol). Based on eGFR and ACR, patients were classified into CKD risk categories according to the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.²¹

CMR and CFD Evaluation of Hemodynamic Adequacy of the Fontan Circulation

All CMR examinations were performed on a 3T system (Ingenia, Philips Healthcare, Best, the Netherlands). The protocol included flow imaging using 2-dimensional real-time phase contrast flow CMR at the level of the inferior vena cava (IVC), superior vena cava (SVC), and the conduit, and 2-dimensional ECG-gated phase contrast CMR at the level of the right pulmonary artery

and left pulmonary artery. Hepatic vein flow was determined indirectly by subtracting IVC flow from conduit flow. All patients also underwent 4-dimensional flow CMR imaging of the TCPC, covering the area between the conduit, SVC, and both pulmonary arteries. Acquisition details are described in detail in previous studies.^{10–15}

Functional Vessel Size

The TCPC geometry was automatically divided into standardized segments (conduit, SVC, right pulmonary artery, and left pulmonary artery).¹² The cross-sectional area (CSA) of these segments was determined perpendicular to the centerline at 1-mm intervals. The CSA of the inlet extensions were reported for the subhepatic IVC and hepatic veins. The CSA_{mean} of each vessel was normalized for the flow rate (mm²/L/min) in each vessel as a marker of functional vessel CSA.

IVC–Conduit Velocity Mismatch Factor

The IVC–conduit velocity mismatch factor was determined for the average respiratory cycle from 2-dimensional real-time CMR measurements as follows: $V_{\text{conduit}}/V_{\text{IVC}}$, where V is the mean velocity in the conduit and subhepatic IVC, respectively. A mismatch factor of 1 represents equal mean velocity (ideal), <1 represents a decrease in mean velocity (oversized conduit), and >1 represents an increase in mean velocity (undersized conduit).¹¹

Four-Dimensional Flow CMR Energetic Analysis

Both the kinetic energy and viscous energy loss of blood flow in the entire TCPC ($n=21$) were computed from the 4-dimensional flow CMR velocity field.¹⁵ Kinetic energy represents the amount of energy in the blood flow due to its motion. Energy loss represents the rate of kinetic energy lost in the blood flow due to friction and can be computed from 3-dimensional velocity gradients derived from 4-dimensional flow CMR. Energetics were normalized for inflow (SVC+Fontan tunnel flow, in L/min); $K\text{Enorm_flow}$ in mJ per L/min and $EL\text{norm_flow}$ in mW per L/min.

Computational Fluid Dynamics

A 3D TCPC model was created from sagittal and transverse 2-dimensional anatomical images as previously described,¹¹ covering the area between the subhepatic IVC, hepatic veins, SVC, and right pulmonary artery (including the right upper lobe branches) and left pulmonary artery up to the level of the segmental branches. The TCPC model was smoothed, centerlines were derived, and vessel extensions were added at all inlets and outlets.

Pulsatile, respiratory cycle–resolved blood flow simulations were performed as previously described, during both resting and increased flow conditions mimicking exercise (ICEM version 17.1; ANSYS Inc., Canonsburg, PA).¹¹ To simulate increased flow during exercise, resting time–resolved flow rates were increased by a factor of 2.44 (both subhepatic IVC and hepatic veins) and 1.67 (SVC) as derived from the literature.²² A detailed description of the CFD methodology is provided in a previous study.¹¹

Power loss (in milliwatts) in the blood flow in the TCPC was determined using the viscous dissipation rate method.²³ Power loss–based pressure gradient (mmHg) from the inlets toward the outlets was determined as follows:

$$\Delta P_{\text{TCPC}} = \frac{PL}{Q_s}$$

where PL and Q_s are the total power loss and the total systemic venous return in the corresponding respiratory phase, respectively.

The resistance normalized for body surface area (in mmHg/L per min per m^2) was determined as follows²⁴:

$$\text{Normalized resistance} = \frac{\Delta P_{\text{TCPC}}}{\frac{Q_s}{\text{Body surface area}}}$$

Statistical Analysis

Continuous variables were checked for normality using the Shapiro–Wilk test and were reported as mean±SD or median (interquartile range [IQR]), accordingly. Categorical variables were reported as frequencies and percentages. Summary data both for the entire cohort and for groups based on eGFR (≥ 90 mL/min per $1.73 m^2$ versus < 90 mL/min per $1.73 m^2$) and ACR (A1 versus A2/A3) were presented. For categorical variables, groups were compared using the chi-squared test or Fisher's exact test, as appropriate, and the resulting *P* values were presented. For all other variables (including continuous demographics, clinical characteristics, and CMR- and CFD-derived metrics), eGFR and ACR were treated as continuous data and Pearson's and Spearman's correlations were used to investigate bivariate correlations with parametric and nonparametric variables, respectively; the correlation coefficient (*r*) and its corresponding *P* value were presented. Prior to calculating these correlations, ACR and resistance were normalized by means of log transformation. A power analysis (G*Power, version 3.1.9.7) revealed that effect sizes of $w > 0.39$ (for 2 categories) or $w > 0.43$ (for 3 categories) and $|r| > 0.30$ were needed to achieve significance for the categorical independent group and continuous bivariate correlation tests, respectively. Finally, linear regression was used to estimate the average eGFR decline rate and

ACR increase rate per year. All analyses were completed with R Statistical Software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

A total of 53 patients with a Fontan circulation who were prospectively evaluated using comprehensive 2-dimensional and 4-dimensional flow CMR and CFD assessment of the Fontan circulation as well as standard laboratory kidney assessment were included in this analysis. Table 1 summarizes key demographic and clinical characteristics of the study population. The median age of the participants at the time of evaluation was 16.2 years (IQR, 14.0–18.9), and 52.8% were men. Average Fontan duration was 13.5 ± 4.7 years at this point. The majority had a dominant left ventricle (56.6%), and 32.1% had a dominant right ventricle. The extracardiac conduit was the predominant type of Fontan palliation (92.5%), and 62.3% had a fenestration at the time of Fontan completion.

Prevalence of Kidney Disease Among Patients With a Fontan Circulation

The average eGFR was 107 ± 18.8 mL/min per $1.73 m^2$, and the median ACR was 2.10 (0.90–4.90) mg/mmol. Reduced kidney function (eGFR < 90 mL/min per $1.73 m^2$) was observed in 11 patients (20.8%), ranging from 75 to 89 mL/min per $1.73 m^2$. Microalbuminuria (A2, 3–30 mg/mmol) was observed in 19 patients (35.8%) and macroalbuminuria (A3, > 30 mg/mmol) in 2 patients (3.8%). Combining these results, 60.4% were classified as having low risk of CKD progression, 35.8% as having moderately increased risk, and 3.8% as having high risk (Figure 1). Linear regression analysis estimated an average eGFR decline rate of -1.83 mL/min per $1.73 m^2$ per year (95% CI, -2.67 to -0.99 ; $P < 0.001$), while ACR showed an increase of $+0.50$ mg/mmol per year (95% CI, $+0.17$ to $+0.83$; $P = 0.004$).

Correlations of Demographic and Clinical Characteristics With eGFR and ACR

Significant negative correlations with eGFR were found for the following demographics: age at examination ($r = -0.52$, $P < 0.001$), time since Fontan procedure ($r = -0.60$, $P < 0.001$), and body surface area at examination ($r = -0.64$, $P < 0.001$) (Table 1, Figure 2). Age at examination correlated positively and significantly, although to a lesser extent, with ACR ($r = 0.29$, $P = 0.034$), while the correlations with time since Fontan and body surface area at examination were not significant (both $P > 0.05$). Ejection fraction was

Table 1. Key Demographic and Clinical Characteristics in the Entire Study Cohort and According to eGFR and ACR Groups

Variable	All patients (N=53)	eGFR ≥90 mL/min per 1.73 m ² (N=42)	eGFR <90 mL/min per 1.73 m ² (N=11)	Correlation coefficient (r)	P value	A1 (N=32)	A2/A3 (N=21)	Correlation coefficient (r)	P value
Male sex, n (%)	28 (52.8)	23 (54.8)	5 (45.5)	...	0.833	19 (59.4%)	9 (42.9)	...	0.370
Age at examination, y	16.2 (14.0–18.9)	15.9 (13.7–17.9)	17.4 (15.8–25.4)	–0.52*	<0.001*	15.3 (13.6–16.8)	17.8 (16.3–22.8)	0.29*	0.034*
Time since Fontan procedure, y	13.4±4.72	12.5±4.37	16.7±4.66	–0.60*	<0.001*	12.5±4.48	14.8±4.86	0.23	0.104
Body surface area at examination, m ²	1.62±0.27	1.57±0.26	1.83±0.23	–0.64*	<0.001*	1.59±0.30	1.68±0.22	0.095	0.499
Dominant ventricle				...	0.700			...	0.401
Biventricular/Indeterminate, n (%)	6 (11.3)	5 (11.9)	1 (9.09)			5 (15.6)	1 (4.76)		
Left ventricle	30 (56.6)	25 (59.5)	5 (45.5)			16 (50.0)	14 (66.7)		
Right ventricle	17 (32.1)	12 (28.6)	5 (45.5)			11 (34.4)	6 (28.6)		
Fontan type, n (%)				...	0.187			...	1.000
Lateral tunnel	4 (7.55)	2 (4.76)	2 (18.2)			2 (6.25)	2 (9.52)		
Extracardiac conduit	49 (92.5)	40 (95.2)	9 (81.8)			30 (93.8)	19 (90.5)		
Conduit size, n (%)				...	0.118			...	0.322
16 mm	26 (53.1)	20 (50.0)	6 (66.7)			15 (50.0)	11 (57.9)		
18 mm	18 (36.7)	17 (42.5)	1 (11.1)			13 (43.3)	5 (26.3)		
20 mm	5 (10.2)	3 (7.50)	2 (22.2)			2 (6.67)	3 (15.8)		
Fenestration at the Fontan operation, n (%)	33 (62.3)	27 (64.3)	6 (54.5)	...	0.728	25 (78.1)	8 (38.1)	...	0.008*
Ejection fraction on CMR, %	48.4±6.65	49.4±6.38	44.3±6.37	0.33*	0.017*	49.6±6.73	46.4±6.19	–0.27*	0.049*
AVV regurgitation grade based on echocardiography, n (%)				...	1.000			...	0.345
None or mild	37 (86.0)	30 (85.7)	7 (87.5)			27 (90.0)	10 (76.9)		
Moderate	6 (14.0)	5 (14.3)	1 (12.5)			3 (10.0)	3 (23.1)		
NYHA class, n (%)				...	0.555			...	0.356
I	33 (62.3)	26 (61.9)	7 (63.6)			21 (65.6)	12 (57.1)		
II	18 (34.0)	15 (35.7)	3 (27.3)			9 (28.1)	9 (42.9)		
III	2 (3.77)	1 (2.36)	1 (9.09)			2 (6.25)	0 (0.00)		

Correlations with eGFR and ACR as continuous variables are shown when appropriate (ie, when the characteristic was also a continuous variable). A1 refers to no albuminuria (<3 mg/mmol), whereas A2 and A3 refer to microalbuminuria (3–30 mg/mmol) and macroalbuminuria (>30 mg/mmol), respectively. ACR indicates albumin-to-creatinine ratio; AVV, atrioventricular valve; CMR, cardiovascular magnetic resonance imaging; eGFR, estimated glomerular filtration rate; and NYHA, New York Heart Association.

*Indicates significant results.

				Persistent albuminuria categories, description and range			Total
				A1	A2	A3	
				Normal to midly increased	Moderately increased	Severely increased	
				<3 mg/mmol	3-30 mg/mmol	>30 mg/mmol	
GFR categories (mL/min/1.73m ²), description and range	G1	Normal or high	≥90	26 (49.1%)	16 (30.2%)	0 (0.0%)	42 (83.0%)
	G2	Mildly decreased	60-89	6 (11.3%)	3 (5.7%)	2 (3.8%)	11 (20.8%)
	G3a	Mildly to moderately decreased	45-59	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	G3b	Moderately to severely decreased	30-44	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	G4	Severely decreased	15-29	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	G5	Kidney failure	<15	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total				32 (60.4%)	19 (35.8%)	2 (3.8%)	53 (100%)

Figure 1. Distribution of chronic kidney disease risk groups among the study participants. Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. CKD risk categories derived from the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.²¹ CKD indicates chronic kidney disease; GFR, glomerular filtration rate; and KDIGO, Kidney Disease: Improving Global Outcomes.

positively correlated with eGFR ($r=0.33$, $P=0.017$) and negatively correlated with ACR ($r=-0.27$, $P=0.049$). Finally, albuminuria (A2/A3) was associated with lower proportions of fenestration at the time of the Fontan operation (38.1% versus 78.1%; $P=0.008$) and lower systemic ventricular ejection fraction at the time of CMR assessment ($46.4\pm6.2\%$ versus $49.6\pm6.7\%$; $P=0.049$). No significant associations

with other demographic and clinical characteristics were observed.

Correlations of CMR- and CFD-Derived Metrics With eGFR and ACR

Summary statistics and correlations for the CMR and CFD derived metrics are presented in Table 2, and

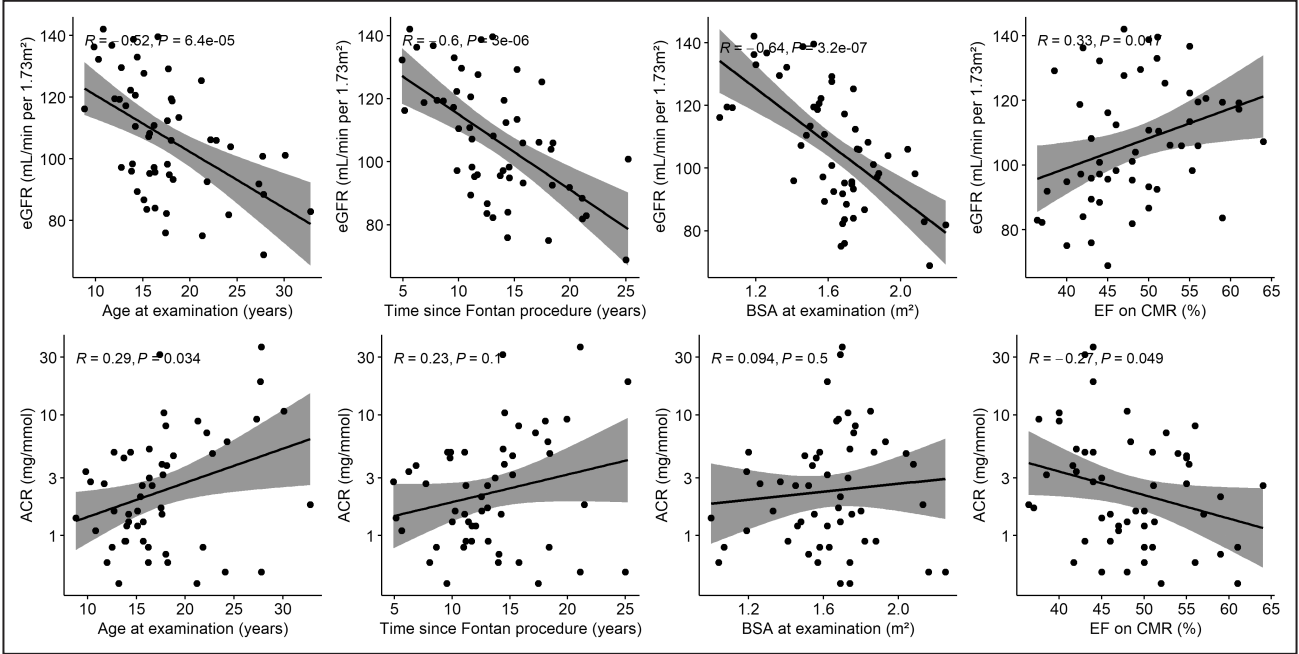


Figure 2. Correlations of key demographic and clinical characteristics with eGFR and ACR. ACR indicates albumin-to-creatinine ratio; BSA, body surface area; CMR, cardiovascular magnetic resonance imaging; EF, ejection fraction; and eGFR, estimated glomerular filtration rate.

Table 2. Correlations of CMR- and CFD-Derived Metrics With eGFR and ACR

Variable	All patients (N=53)	eGFR ≥90 mL/min per 1.73 m ² (N=42)	eGFR <90 mL/min per 1.73 m ² (N=11)	Correlation coefficient (r)	P value	A1 (N=32)	A2/A3 (N=21)	Correlation coefficient (r)*	P value
2-dimensional phase contrast CMR-derived metrics									
Functional vessel size (CSA indexed to flow)									
SVC, mm ² /[L/min]	181±63.2	179±55.7	190±93.6	−0.16	0.309	169±68.3	196±53.2	0.23	0.131
Conduit, mm ² /[L/min]	63.6 (53.5–88.9)	62.0 (52.7–94.1)	66.9 (61.8–71.6)	0.32 [§]	0.038 [§]	63.6 (54.2–88.2)	63.1 (51.5–86.9)	−0.18	0.242
IVC, mm ² /[L/min]	147 (124–172)	147 (124–175)	152 (122–163)	0.03	0.851	141 (116–165)	150 (132–175)	0.22	0.159
Hepatic vein, mm ² /[L/min]	243 (181–347)	242 (170–347)	272 (224–346)	0.21	0.187	247 (207–344)	242 (177–351)	−0.07	0.654
Right pulmonary artery, mm ² /[L/min]	104 (86.0–136)	105 (83.0–136)	102 (98.4–128)	0.01	0.962	106 (87.1–136)	98.2 (85.7–117)	0.02	0.876
Left pulmonary artery, mm ² /[L/min]	105 (88.3–145)	106 (88.3–148)	97.9 (83.7–121)	0.07	0.651	100 (83.7–134)	111 (93.6–158)	0.11	0.457
IVC–conduit velocity mismatch factor	2.00±0.70	1.99±0.75	2.07±0.50	−0.35 [§]	0.022 [§]	1.92±0.76	2.12±0.61	0.20	0.188
4-dimensional flow CMR-derived metrics†									
Kinetic energy indexed to flow, mJ/[L/min]	0.28±0.06	0.27±0.07	0.28±0.06	−0.59 [§]	0.005 [§]	0.28±0.07	0.27±0.06	−0.06	0.812
Energy loss rate indexed to flow, mW/[L/min]	0.08±0.02	0.08±0.02	0.07±0.01	−0.38	0.091	0.08±0.02	0.08±0.03	−0.10	0.661
CFD-derived metrics									
TCPC resistance, at rest, mmHg/[L/min/m ²]	0.23 (0.18–0.28)	0.23 (0.16–0.28)	0.26 (0.22–0.32)	−0.42 ^{‡,§}	0.005 [§]	0.23 (0.18–0.27)	0.26 (0.18–0.32)	0.13	0.412
TCPC resistance, during exercise, mmHg/[L/min/m ²]	0.32±0.13	0.32±0.14	0.36±0.10	−0.43 ^{‡,§}	0.004 [§]	0.30±0.11	0.36±0.16	0.20	0.192

A1 refers to no albuminuria (<3mg/mmol), whereas A2 and A3 refer to microalbuminuria (3–30mg/mmol) and macroalbuminuria (>30mg/mmol), respectively. ACR indicates albumin-to-creatinine ratio; CFD, computational fluid dynamics; CMR, cardiovascular magnetic resonance; CSA, cross-sectional area; eGFR, estimated glomerular filtration rate; IVC, inferior vena cava; SVC, superior vena cava; and TCPC, total cavopulmonary connection.

*The y axis (ie, ACR) was log-transformed to calculate the correlations.

†The total TCPC without device-related CMR artefacts was available for 4-dimensional flow energetic analysis in 21 of 53 patients (39.6%).

‡The x axis (ie, CMR metric) was log-transformed to calculate the correlations.

§Indicates significant results.

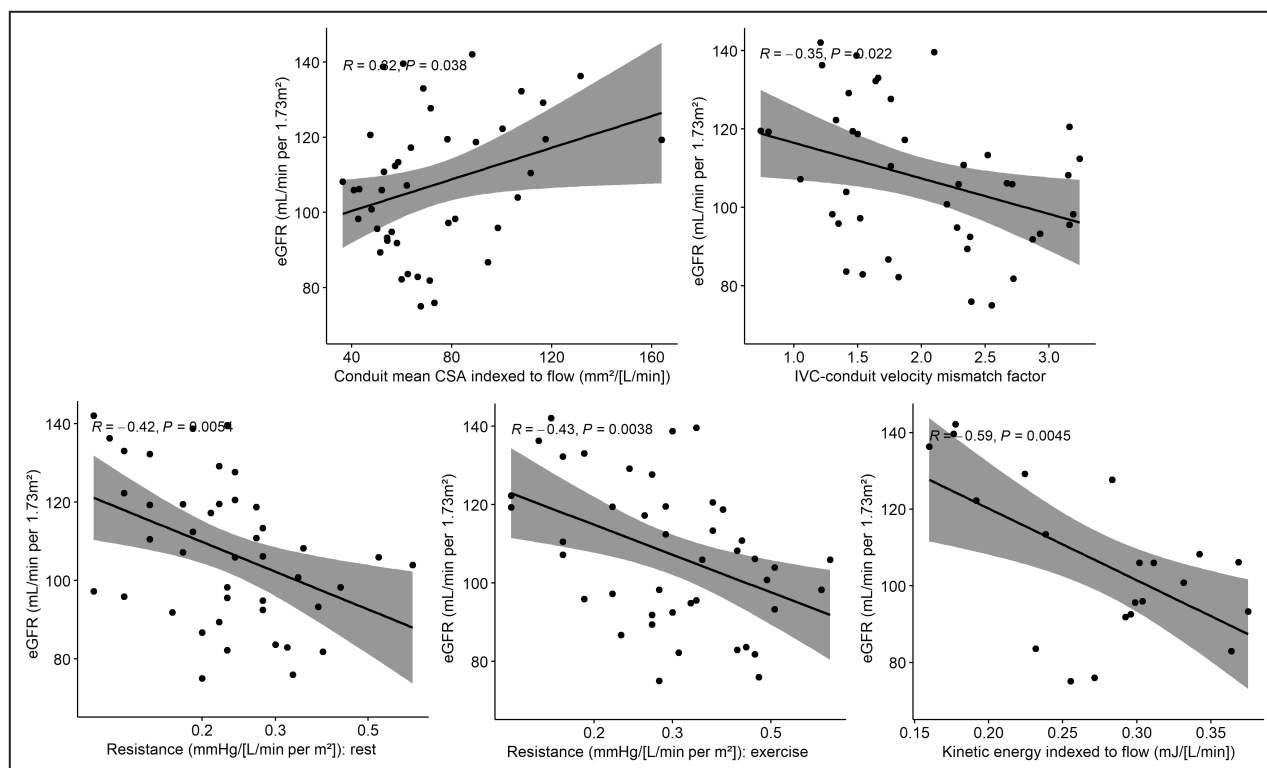


Figure 3. Significant correlations of CMR- and CFD-derived metrics with eGFR and ACR.

The full set of correlations are presented in [Figures S1 through S6](#). The data for kinetic energy indexed to flow are based on the data of 21 of 53 patients (39.6%), because the total TCPC without device-related CMR artefacts was available for 4-dimensional flow energetic analysis only in a subset of our population. ACR indicates albumin-to-creatinine ratio; CFD, computational fluid dynamics; CMR, cardiovascular magnetic resonance imaging; CSA, cross-sectional area; eGFR, estimated glomerular filtration rate; and IVC, inferior vena cava.

plots for significant correlations are given in [Figure 3](#); plots for all correlations are given in [Figures S1–S6](#).

Correlations With 2-Dimensional Phase Contrast CMR-Derived Metrics

The median CSA of the conduit indexed to flow (functional conduit size) was 63.6 (53.5–88.9) mm²/[L/min] and showed a positive, significant correlation with eGFR ($r=0.32$, $P=0.038$) but not with ACR ([Table 2](#), [Figures S1–S6](#)). No significant correlations with either eGFR or ACR could be demonstrated for the functional vessel size of the other vessels of the TCPC.

The mean IVC–conduit velocity mismatch factor was 2.00 ± 0.70 , indicating a 2-fold increase of the mean velocity from the subhepatic IVC toward the conduit ([Table 2](#), [Figures S3 and S4](#)). The mismatch factor was significantly, negatively correlated with eGFR ($r=-0.35$, $P=0.022$) but not with ACR.

Correlations With 4-Dimensional Flow CMR-Derived Metrics

The total TCPC without device-related CMR artifacts was available for 4-dimensional flow energetic analysis

in 21/53 patients (39.6%). In these patients, the mean kinetic energy indexed to flow was 0.28 ± 0.06 mJ/[L/min] and the energy loss indexed to flow was 0.08 ± 0.02 mW/[L/min] ([Table 2](#), [Figures S5 and S6](#)). Kinetic energy indexed to flow was significantly negatively correlated with eGFR ($r=-0.59$, $P=0.005$) but not with ACR ($r=-0.06$, $P=0.812$). Energy loss indexed to flow also tended to show a negative association with eGFR, but this effect did not reach statistical significance ($r=-0.38$, $P=0.091$).

Correlations With CFD-Derived Metrics

Based on CFD modeling, the resistance across the TCPC was a median of 0.23 (IQR, 0.18–0.28) mmHg/[L/min per m²] at rest and a mean of 0.32 ± 0.13 mmHg/[L/min per m²] at exercise. Resistance was significantly, negatively correlated with eGFR, both at rest ($r=-0.42$, $P=0.005$) and with simulated exercise ($r=-0.43$, $P=0.004$) but not with ACR ([Table 2](#), [Figures S3 and S4](#)).

DISCUSSION

This study of 53 ambulatory patients with a Fontan circulation provides the first comprehensive summary

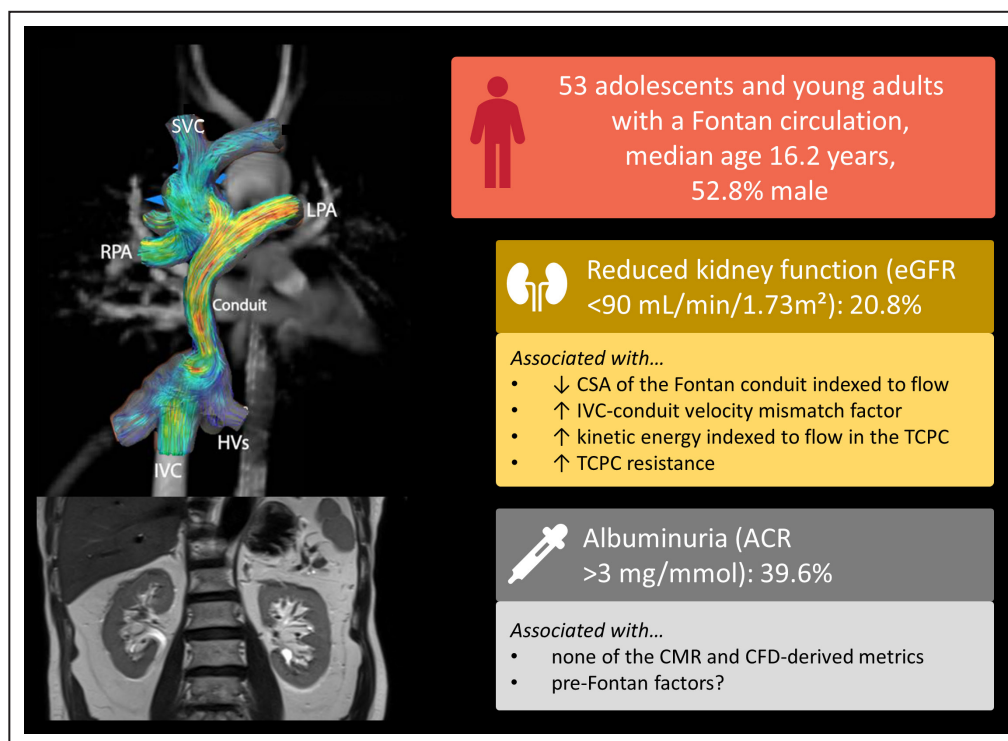


Figure 4. Summary of the study findings.

ACR indicates albumin-to-creatinine ratio; CFD, computational fluid dynamics; CMR, cardiovascular magnetic resonance; CSA, cross-sectional area; eGFR, estimated glomerular filtration rate; HVs, hepatic veins; IVC, inferior vena cava; LPA, left pulmonary artery; RPA, right pulmonary artery; SVC, superior vena cava; and TCPC, total cavopulmonary connection.

of the intricate relationship between demographic factors, kidney disease (based on eGFR and ACR), and Fontan hemodynamics (based on advanced 2-dimensional and 4-dimensional flow CMR metrics and CFD) (Figure 4). We demonstrated that reduced kidney function and albuminuria occurs in 20.8% and 39.6%, respectively, of clinically well adolescents and young adults with a Fontan circulation. Furthermore, we identified clinical and hemodynamic correlates of eGFR and ACR. Most notably, lower CSA of the Fontan conduit indexed to flow, higher IVC–conduit velocity mismatch factor, higher kinetic energy indexed to flow in the TCPC, and higher TCPC resistance were all associated with lower eGFR but not with albuminuria. Collectively, our findings suggest that adverse Fontan-hemodynamics not only link to liver disease but also play a role in renal disease. Therefore, this study contributes to our understanding of the pathophysiology of kidney disease in patients with a Fontan circulation and offers potential targets for intervention to improve kidney health in this population.

CKD in Patients With a Fontan Circulation

Our study emphasizes that CKD is common among patients with a Fontan circulation, even in a contemporary and clinically well cohort of adolescents and young

adults. About 50.9% of our cohort either had reduced kidney function (20.8%) or albuminuria (39.6%). The fact that these disease markers were apparent even before any other signs of systemic dysfunction (eg, plastic bronchitis, protein-losing enteropathy, heart failure, arrhythmias) suggests that kidney disease may not only be the second most prevalent—next to thyroid disease—but also is one of the earliest manifestations of Fontan failure. Of interest, the majority of patients met the diagnosis of CKD because of albuminuria, a result consistent with other studies.²⁵ Albuminuria is considered an early sign of kidney dysfunction, even in the presence of normal eGFR, and has been shown an independent risk factor for progressive GFR decline.²⁶ Given the eGFR decline rate of -1.83 mL/min per 1.73m^2 per year, it is expected that as these patients age, progressively more of them will develop reduced kidney function.

The assessment of kidney function has witnessed various methodologies over time. Historically, these methodologies have largely relied on serum creatinine levels, often employing formulas such as the bedside Schwartz equation, the Modification of Diet in Renal Disease equation, or the standard CKD-EPI equation.⁸ In congruence with these past approaches, our current study also employed a creatinine-based method.

However, our investigation uniquely adopted the refined CKD-EPI40 equation, acknowledged for its superior precision in estimating kidney function among pediatric and adolescent populations. Furthermore, the CKD-EPI40 does not rely on height, which is often smaller given somatic growth restriction and incomplete catch-up growth in patients with a Fontan circulation.²⁷ This enhancement in accuracy is illustrated through comparison with a recent study by Katz et al,²⁸ wherein the bedside Schwartz equation identified reduced kidney function in a mere 11% of patients with a Fontan circulation. In contrast, our present study, despite dealing with a marginally younger cohort (median age, 16 years versus 19 years), identified twice the number of affected patients, underscoring the tangible advantages of embracing the CKD-EPI40 equation.

To date, only 3 studies have published “measured” measured glomerular filtration rate (mGFR) using ^{99m}Tc-DTPA renal dynamic imaging, the current gold standard for assessing kidney function, in patients with a Fontan circulation.^{25,29,30} Collectively, these studies have estimated the prevalence of reduced kidney function (mGFR <90 mL/min per 1.73 m²) to be 25% at a mean age of 12 years, 37% at a mean age of 20 years, and 45% to 53% at a mean age of 28 years. Assuming a linear progression over time, the expected prevalence within our cohort (median age, 16 years) would theoretically have stood at 31%, thereby indicating that our eGFR measurements still underestimated 10% of cases. Indeed, during the development of the creatinine-based CKD-EPI equation it has been shown that eGFR overestimates mGFR (and thus downgrades the severity of kidney dysfunction) by 6.6 (IQR, 3.5–9.2) mL/min per 1.73 m² in the 60–89 mL/min per 1.73 m² range and by 11.1 (IQR, 8.0–12.5) mL/min per 1.73 m² in the ≥90 mL/min per 1.73 m² range.³¹ Imprecision of eGFR measurements, as expressed as the IQR of the difference between measurements, is 15.4 (IQR, 14.3–16.5) mL/min per 1.73 m² and can also lead to discordant results between eGFR and mGFR as has commonly been reported in the literature. Furthermore, it has been suggested that creatinine-based eGFR methods would overestimate mGFR in patients with a Fontan circulation because of its reliance on skeletal muscle mass,^{28,29} which is known to be reduced in these patients.³² Cystatin C–based methods have been proposed to circumvent this issue; however, the applicable equations designed for the pediatric and adolescent demographic only became available after our study’s enrollment phase.³³ Consequently, these measurements were not available in our data sets. As we pivot toward the future, it is prudent to acknowledge that these cystatin C–based techniques should take precedence in subsequent research and clinical applications. Nevertheless, it should be underscored that, for inquiries akin to those posed within our

present investigation, creatinine-based methods retain their relevance and utility.

Insights Into the Determinants of eGFR in Patients With a Fontan Circulation

Our analyses revealed the following factors to be important determinants of eGFR in patients with a Fontan circulation: lower CSA of the Fontan conduit indexed to flow, higher IVC–conduit velocity mismatch factor, higher kinetic energy indexed to flow in the TCPC, and higher resistance across the TCPC. This suggests that Fontan conduits that exhibit excessive restrictiveness due to somatic growth not only result in amplified energy dissipation but also contribute to the deterioration of kidney function. The underlying mechanisms driving this phenomenon are likely linked to elevated central venous pressures and subsequent venous congestion within the kidney parenchyma. The association between venous congestion and kidney function finds its roots in seminal studies conducted by Damman et al¹⁷ and Mullens et al.¹⁸ Their work, particularly in patients experiencing acute decompensated heart failure, revealed a pivotal role played by increased central venous pressure in tandem with diminished kidney blood flow, collectively dictating glomerular filtration rate and the overall decline of kidney function. Interestingly, these studies indicated that cardiac index did not hold the same degree of influence.

Recently, Boorsma et al³⁴ have proposed the “kidney tamponade hypothesis” to provide a coherent framework for the underlying pathophysiology. This concept stems from the anatomic reality of the kidney being encased in a rigid, fibrous capsule. Consequently, elevated venous pressures induce a direct translation into elevated interstitial pressures, triggering compression of essential kidney structures including tubules, venules, and glomeruli. Given the increased pressure in the proximal tubule and Bowman’s space, the filtration gradient across the glomerular membrane is considerably reduced, thereby compromising GFR. Considering the chronic impairment of lymphatic drainage that characterizes patients with a Fontan circulation, this predicament is further exacerbated. The compromised drainage exacerbates the challenges posed by kidney tamponade, as it curtails effective volume drainage from the kidney. In this intricate interplay of factors, the issue of kidney tamponade is compounded, subsequently perpetuating the decline in kidney function.

Currently, the prevailing practice involves finalizing the Fontan circulation when children reach the ages of 3 to 5 years, using extracardiac conduits with an approximate diameter of 16 mm. However, it is important to note that the heart undergoes substantial growth in the years following Fontan completion, often leading

to a scenario where these conduits become inherently undersized. Extensive research conducted by our group^{11,12,16} has previously demonstrated the detrimental impact of this undersizing on Fontan hemodynamics. Recent efforts have therefore been focused on either providing larger conduits at the time of the initial Fontan procedure, or expanding Fontan conduits during follow-up.^{35,36} Whether such interventions may yield improved kidney outcomes remains to be seen. In the meantime, careful investigation to exclude reversible impediments to the passive pulmonary blood flow in the form of thrombi, stenosis, and valve regurgitation seems advisable for all patients with a Fontan circulation to improve overall outcomes.

Insights Into the Determinants of ACR in Patients With a Fontan Circulation

ACR has been associated with death in patients with a Fontan circulation, independently from eGFR.²⁶ Interestingly, the same factors that determined eGFR were not associated with ACR. Nonetheless, albuminuria was highly prevalent among patients with a Fontan circulation, even during very early follow-up after the procedure. It is therefore possible that albuminuria is driven by other factors, some of which might even occur before or directly after the Fontan procedure.

Contrary to commonly held beliefs, albuminuria does not result from cracks in the glomerular membrane.³⁷ Under normal physiological conditions, large amounts of albumin undergo filtration. Subsequent to this filtration process, 2 pathways within the proximal tubular cells come into play: One involves a recovery mechanism that reabsorbs albumin into the peritubular blood supply, while the other engages a lysosomal degradation pathway that transforms albumin into small peptide fragments, ultimately excreted in the urine. Dysfunction of the latter pathway can lead to albuminuria below the nephrotic range and is related to various metabolic disturbances such as neurohormonal upregulation (in particular, angiotensin II and transforming growth factor- β 1), hypertension, hyperglycemia, and inflammation. A number of these disturbances manifest in patients on a Fontan trajectory, such as chronic cyanosis, volume/pressure overload, stress induced by repeated surgeries and prolonged hospital stays, and malnutrition, among other factors. Recent research by Ohuchi et al²⁶ has pinpointed elevated aortic systolic pressure and increased glycated hemoglobin levels as correlates of albuminuria in patients with a Fontan circulation. Additionally, chronic cyanosis and univentricular heart conditions have been associated with multiple indicators of tubular injury.³⁸

In our study, the presence of a fenestration at the Fontan operation was associated with lower ACR. Of note, virtually all fenestrations either closed

spontaneously or through an interventional procedure from 6 months after the Fontan operation, such that any beneficial effect of a fenestration must be situated within this time frame. The inclusion of a fenestration in the Fontan procedure facilitates circuit decompression and may augment cardiac output at equivalent Fontan pressure. This attribute has been linked to several favorable short-term outcomes, including lower rates of pleural drainage, shorter hospital length of stay, and reduced need for additional postoperative procedures.³⁹ This collective impact likely contributes to the mitigation of stress surrounding the Fontan procedure, thereby potentially exerting a positive influence on the preservation of the lysosomal degradation pathway within the proximal tubule. In a parallel manner, enhanced myocardial function, as evidenced by higher systemic ventricular ejection fraction on CMR, appears to confer protection against the development of albuminuria.

Implications for Practice and Future Research

Our research underscores the paramount significance of instituting early and structured follow-up protocols for kidney disease among individuals with a Fontan circulation. It is imperative to conduct regular assessments employing methodologies aligned with the Kidney Disease: Improving Global Outcomes guidelines,²¹ a practice that is ideally instated during childhood. Current recommendations concerning risk-stratified referrals for nephrology services indicate that within our cohort, 35.8% of patients would benefit from eConsult (due to a moderately increased risk of CKD progression), while 3.8% necessitate nephrology referral (due to a high risk of CKD progression).⁴⁰ Furthermore, cultivating a heightened awareness of factors influencing eGFR (such as resistance across the TCPC circuit and venous congestion) and ACR (including cyanosis, inflammation, neurohormonal upregulation, hypertension, and hyperglycemia) is pivotal to effectively enhancing kidney health in this patient population.

Although eGFR and ACR play pivotal roles in diagnosing CKD, they offer an incomplete view of the entire spectrum of kidney injury. Recognizing this limitation, recent years have witnessed the emergence of novel serum and urine biomarkers for kidney injury, among them kidney injury molecule-1, N-acetyl- β -D-glucosidase, and neutrophil gelatin-related lipid transporter protein. These biomarkers have demonstrated utility in diagnosis, monitoring, and clinical decision-making across diverse contexts. Initial findings within the Fontan population are promising, although further research is requisite to translate these findings into clinical practice.²⁸

Limitations

These findings must be interpreted within the context of the underlying study design. First, samples of patients with a Fontan circulation are often heterogeneous, because the low prevalence of this condition often warrants pooling of patients with different underlying anatomies and clinical pathways. Second, while participants were enrolled in a prospective manner, certain analyses hinged upon the availability of clinically ordered tests. Notably, the inclusion of cystatin C as an analytical parameter was impeded due to its nonroutine use during the participant inclusion period, resulting in its omission from our data set. Similarly, Tc-99m diethylenetriamine pentaacetate measurements were not available. Furthermore, it is common practice for studies, including our own, to rely on a single estimation of eGFR, whereas a clinical diagnosis of CKD requires the recording of reduced kidney function on multiple measurements over at least 3 months.²¹ Given the lack of adjustment for multiple testing, prudence is advised during interpretation, particularly concerning statistical significance at the borderline level. Finally, the relatively modest sample size of the cohort curtails the statistical power. In particular, the high occurrence of device-related artefacts in the TCPC conduit substantially restricted the pool of eligible data for the 4-dimensional flow CMR energetic analyses.

CONCLUSIONS

This study suggests that kidney dysfunction, based on eGFR using the improved CKD-EPI40 formula, and albuminuria are common among clinically well adolescents and young adults with a Fontan circulation. Advanced 2-dimensional and 4-dimensional flow CMR and CFD derived metrics indicative of declining Fontan physiological features are associated with eGFR and might serve as targets to improve kidney health in patients with a Fontan circulation. Albuminuria might be driven by other factors that still need to be determined. Future research is warranted on novel biomarkers to improve diagnosis and management of CKD in patients with a Fontan circulation and whether modifying the identified targets, such as Fontan conduit expansion, may help prevent kidney disease in this population.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figures S1–S6.

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